was shaken mechanically for 4 hr. at room temperature. Water (10 ml.), ethyl acetate (10 ml.), and hydrochloric acid (2 ml., 1 *N*) were added, and the mixture was shaken vigorously and filtered through a pad of infusorial earth. The organic phase was washed with water and taken to dryness *in vacuo*, and crystals (31 mg., m.p. 190–195°) were obtained from acetone. Recrystallization from acetone gave 9.1 mg. of product which melted at 196–197.5° and did not depress the melting point of samples of XI which had been prepared from VIII and from I.[2] The infrared spectra of the three samples of XI were identical.

3α,20β-Diacetoxy-11-oxo-5β-pregnan-21-oic Acid (XI) from VIII.—To a solution of 50 mg. of 3α,20β-diacetoxy-21-hydroxy-5β-pregnan-11-one in 5 ml. of acetic acid was added 0.11 ml. of 5 *M* chromic acid in water at room temperature. After 1.5 hr., water was added, the solution was extracted with ethyl acetate, and the organic phase was washed with water and taken to dryness *in vacuo*. Crystals (16 mg., m.p. 196.5–198°; 20 mg., m.p. 192–194.5°) were obtained from acetone. The recrystallized product melted at 198.5–200.5° and did not depress the melting point of the 3α,20-diacetoxy-11-oxo-5β-pregnan-21-oic acid[2] (m.p. 199–200°, $[\alpha]_D$ +41°) which was derived from 3α,-21,21-trihydroxy-5β-pregnane-11,20-dione (the hydrate of I) by treatment with alkali. Furthermore, the infrared spectra of the two diacetoxy acids were identical.

Methyl 3α,20β-Diacetoxy-11-oxo-5β-pregnan-21-oate (XII) from XI.—Treatment of 3α,20β-diacetoxy-11-oxo-5β-pregnan-21-oic acid (derived from VIII) with diazomethane yielded the ester XII, m.p. 200–202°, which did not depress the melting point of methyl 3α,20β-diacetoxy-11-oxo-5β-pregnan-21-oate,[2] m.p. 204–205°. Their infrared spectra were identical.

5β-Pregnane-3α,11β,20β,21-tetrol (XIV) from X.—To 98 mg. of 3α,20β,21-trihydroxy-5β-pregnan-11-one (X) in 5.0 ml. of tetrahydrofuran was added 190 mg. of lithium aluminum hydride in 25 ml. of the same solvent. The solution was refluxed for 30 min. and cooled and the excess $LiAlH_4$ was decomposed with ethyl acetate. The solution was acidified with hydrochloric acid and extracted with ethyl acetate. The extract was washed, the solvent was removed, and crystals (52 mg., m.p. 198–200°) were obtained from acetone. A purified sample had m.p. 207–207.5°, $[\alpha]_D$ +43 ± 2° (CH_3OH); lit.[16] m.p. 203–204°, $[\alpha]_D$ +53° (CH_3OH). This product did not depress the melting point of the tetrol (XIV) prepared by reduction of methyl 3α,20β-dihydroxy-11-oxo-5β-pregnan-21-oate with $LiAlH_4$. The infrared spectra of these two samples of tetrol were identical.

Anal. Calcd. for $C_{21}H_{36}O_4$: C, 71.55; H, 10.29. Found: C, 71.05; H, 10.18.

5β-Pregnane-3α,11β,20β,21-tetrol[17] (XIV) from XIII.—A solution of 190 mg. of methyl 3α,20β-dihydroxy-11-oxo-5β-pregnan-21-oate[2] (m.p. 204–205°) in 5 ml. of tetrahydrofuran (distilled from $LiAlH_4$) was mixed with 190 mg. of $LiAlH_4$ dissolved in 20 ml. of tetrahydrofuran. The mixture was refluxed 30 min. and cooled. The excess of $LiAlH_4$ was decomposed with ethyl acetate. A small volume of concentrated Na_2SO_4 was added and then 12 g. of solid Na_2SO_4 was added. The precipitate was filtered off and washed repeatedly with tetrahydrofuran. The combined filtrate and washings were taken to dryness *in vacuo* and crystals (20 mg., m.p. 197–199°) were obtained from acetone. The product appeared to be homogeneous on chromatography in formamide–chloroform and in toluene–ethyl acetate–methanol–water (16:4:10:10); it migrated at the same rate as 5β-pregnane-3α,11β,20β,21-tetrol and in the latter system, R_f 0.33. After recrystallization from methyl ethyl ketone, the product had m.p. 208.5–209° and it did not depress the melting point of 5β-pregnane-3α,11β,20β,21-tetrol which was derived from X. The infrared spectra of the two samples of XIV were identical.

5β-Pregnane-3α,11β,20β,21-tetrol (XIV) from XV.—To a solution of 1.74 g. of 3α,21-dihydroxy-5β-pregnane-11,20-dione[18] (XV) in 75 ml. of methanol was added 2.0 g. of potassium borohydride in 7.5 ml. of water at room temperature. After 48 hr. the solution was concentrated *in vacuo* to remove most of the methanol, water was added, and the solution was extracted with ethyl acetate. The extract was washed with dilute hydrochloric acid, sodium bicarbonate solution, and water and then taken to dryness. The residue gave 1.42 g. of crude product, m.p. 190–194°, from acetone. During chromatography in isooctane–*t*-butyl alcohol–water (50:25:45), R_f of XIV was 0.62; a minor constituent migrated with R_f 0.56. By recrystallization from methyl ethyl ketone, 527 mg. (30%) of chromatographically pure tetrol (XIV), m.p. 209–209.5°, $[\alpha]_D$ +41 ± 2° (CH_3OH), was obtained.

(16) M. Harnick, *Steroids*, **2**, 485 (1963).

(17) We are indebted to Dr. Marvin L. Lewbart for performing this reduction.

(18) M. L. Lewbart, and V. R. Mattox, *J. Org. Chem.*, **28**, 2001 (1963).

The Synthesis of 3-Alkoxy-*cis*-2-*trans*-4-unsaturated Acids[1]

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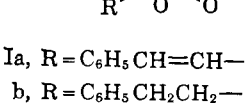
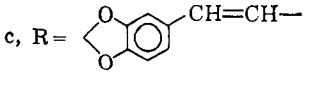
Ethyl β-methoxy-*cis*-crotonate and ethyl β-ethoxy-*cis*-crotonate were conveniently prepared in high yield. The reaction of various aldehydes with these crotonates yielded the corresponding 3-alkoxy-*cis*-2-*trans*-4-unsaturated acids. The ultraviolet and nuclear magnetic resonance spectra of these compounds are discussed.

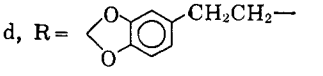
To prepare various constituents of *Piper methysticum* Forst. many workers have utilized the Reformatsky reaction. Kostermans[2] reported the synthesis of *dl*-kawain (Ia) by a condensation of ethyl α-bromo-β-methoxycrotonate and cinnamaldehyde in a yield of less than 10%. Viswanathan and Swaminathan[3] were able to prepare *dl*-dihydrokawain (Ib) in an 8.6% yield by a condensation of ethyl α-bromo-β-methoxycrotonate with hydrocinnamaldehyde. Klohs and coworkers[4] prepared *dl*-methysticin (Ic) in a 38% yield in an analogous manner. Reduction of the racemate Ic



Ia, R = $C_6H_5CH{=}CH-$

b, R = $C_6H_5CH_2CH_2-$





afforded *dl*-dihydromethysticin (Id).[4] The preparation of the bromocrotonate is lengthy and the over-all yield is low.

The approach to the synthesis of dihydrokawain (Ib) and analogs reported herein was essentially a three-step

(1) Taken from the dissertation presented by A. N. Voldeng, Jan., 1964, to the Graduate School of the University of Kansas in partial fulfillment of the requirements for the Ph.D. degree.

(2) D. G. F. R. Kostermans, *Rec. trav. chim.*, **70**, 79 (1951).

(3) K. Viswanathan and S. Swaminathan, *Proc. Indian Acad. Sci.*, **52A**, 63 (1960).

(4) M. W. Klohs, F. Keller, and R. E. Williams, *J. Org. Chem.*, **24**, 1829 (1959).

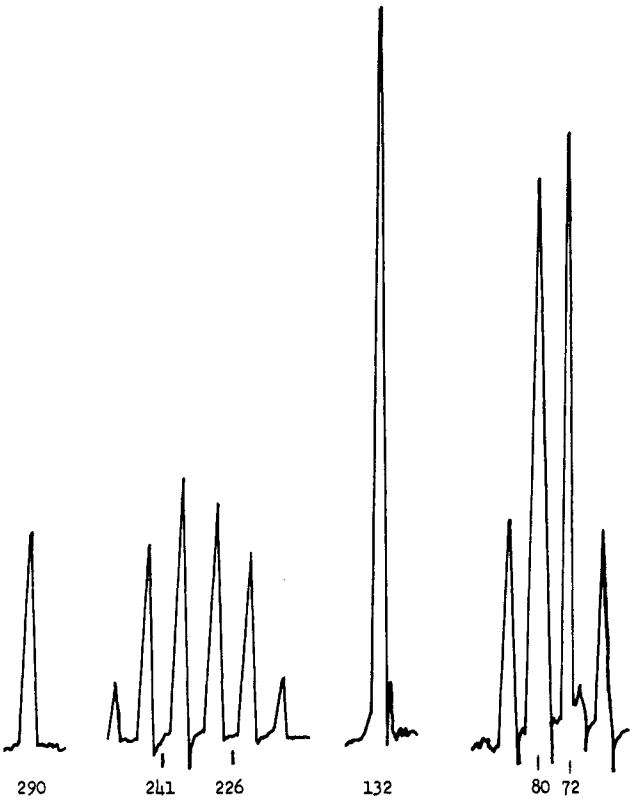


Fig. 1.—N.m.r. spectrum of the ethyl β-ethoxy-*cis*-crotonate determined in carbon tetrachloride (c.p.s.).

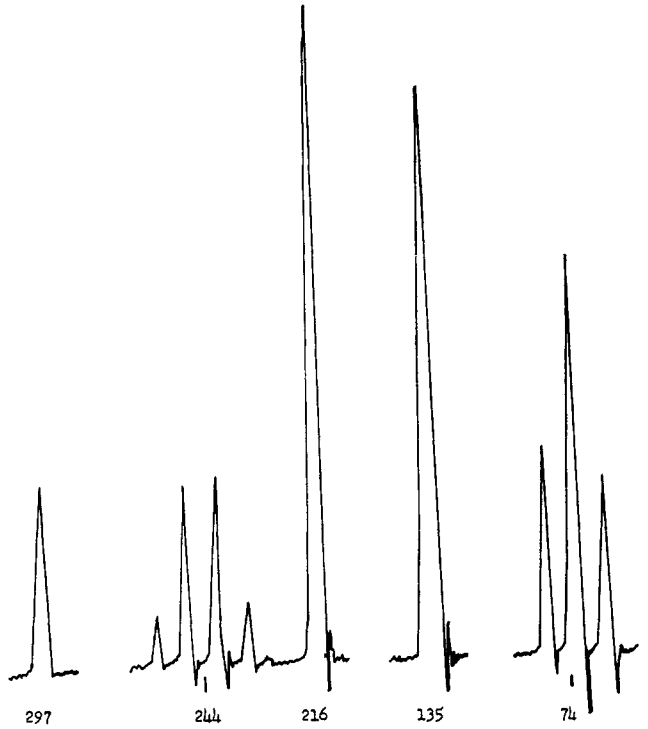


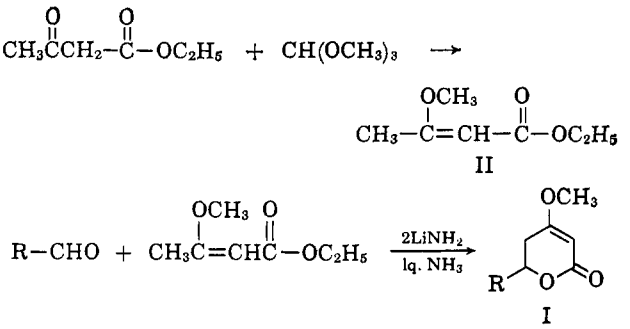
Fig. 2.—N.m.r. spectrum of ethyl β-methoxy-*cis*-crotonate determined in carbon tetrachloride (c.p.s.).

proposal, utilizing readily available starting materials, shown at the top of col. 2.

Hauser and co-workers[5,6] have shown that it is possible to condense lithioacetates with various aldehydes and ketones in a Reformatsky-like reaction. The extra

(5) C. R. Hauser and W. H. Puterbaugh, *J. Am. Chem. Soc.*, **75**, 1068 (1953).

(6) W. R. Dunnavant and C. R. Hauser, *J. Org. Chem.*, **25**, 503 (1960).



equivalent of lithium amide is employed to prevent self-condensation of the ester. Presumably the carbonyl, as well as the alkoxide oxygen of the acetate coordinates with the lithium amide to make the ester an effectively stronger acid.[7]

Ethyl β-methoxycrotonate (II) was considered to be a vinylog of ethyl acetate, and hence the crotonate should undergo a Reformatsky-like reaction with various aldehydes to yield dihydrokawain (Ib) and analogs.

At the time this work was initiated, the only reported preparation of ethyl β-methoxycrotonate (II) was the reaction of diazomethane and ethyl acetoacetate. As large amounts of the crotonate were desired and since this reaction is a lengthy one (3 days) with poor yields (*ca.* 40%), an alternative means of preparing this enol ether was attempted.

Using the conditions of Blaise and Maire,[8] ethyl β-methoxy-*cis*-crotonate (II) was conveniently prepared in 95% yield from ethyl acetoacetate and trimethyl orthoformate. Utilizing the same reaction conditions, ethyl β-ethoxy-*cis*-crotonate (III) was prepared in 88% yield from ethyl acetoacetate and triethyl orthoformate.

The nuclear magnetic resonance (n.m.r.) spectrum, Fig. 1, of the ethoxycrotonate, III, is quite unusual. Both the allylic methyl protons and the olefinic proton appear as singlets, but the methyl and methylene protons of the ether and ester functions appear as multiplets. The difference between the chemical shifts of the methyl protons a and e in III is equal to the coupling constant. Thus the methyl protons a and e appear not as a triplet or unsymmetrical multiplet, but as a symmetrical quadruplet (1:3:3:1).

The difference between the chemical shifts of the methylene protons b and f in III is equal to two times their coupling constant, causing a symmetrical sextet (1:3:4:4:3:1) rather than a quartet or unsymmetrical multiplet.

The n.m.r. spectrum of the methoxycrotonate, II, was complex with many multiplet splittings (Fig. 2).

The chemical shifts for the various protons of the methoxycrotonate (II) are in agreement with those assigned to the ethoxycrotonate (III), as shown in Table I.

TABLE I

CHEMICAL SHIFTS OF ETHYL β-ALKOXY-*cis*-CROTONATES[a]

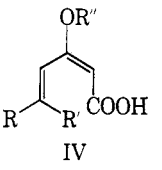
	Proton					
	a	b	c	d	e	f
β-Ethoxy (III)	72	241	290	132	80	226
β-Methoxy (II)	74	244	297	135	216	

[a] Values are given in cycles per second.

(7) W. R. Dunnavant and C. R. Hauser, *ibid.*, **25**, 1693 (1960).

(8) E. E. Blaise and M. Maire, *Ann. chim. phys.*, [8]**16**, 567 (1908).

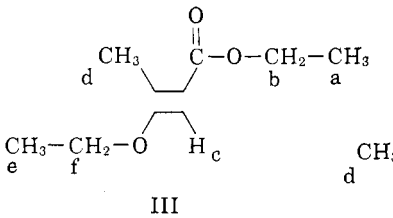
TABLE II



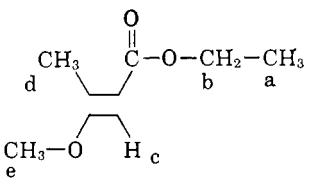
IV

Product	R	R′	R″	M.p., °C. Obsd.	M.p., °C. Lit.	λ_{max}^{EtOH}, mμ (ε) Obsd.	λ_{max}^{EtOH}, mμ (ε) Lit.
a	C_6H_5	H	CH_3	157.5 dec.	173 dec.[a]	229 (13,160) 235 (11,920) 308 (22,600)	229 (17,500)[a] 308 (24,500)[a]
b	C_6H_5	H	C_2H_5	151–152 dec.	153–154 dec.[b]	229 (18,200) 235 (16,500) 310 (29,800)	
c	C_6H_5—CH=CH	H	CH_3	178 dec.	184 dec.[c]	244 (14,830) 251 (15,390) 332 (52,000)	251 (9500)[b] 322 (40,000)[b]
d	C_6H_5	C_6H_5	CH_3	149 dec.			
e	C_6H_5—CH_2—CH_2	H	CH_3	137.5–138 dec.	139–140 dec.[d]		

[a] H. B. Henbeat and E. R. H. Jones, *J. Chem. Soc.*, 3628 (1950). [b] E. B. Reid and W. R. Ruby, *J. Am. Chem. Soc.*, **73**, 1054 (1951). [c] E. M. F. Fowler and H. B. Henbest, *J. Chem. Soc.*, 3624 (1950). [d] W. Borsche and W. Pietzsch, *Ber.*, **63**, 2414 (1930).



III

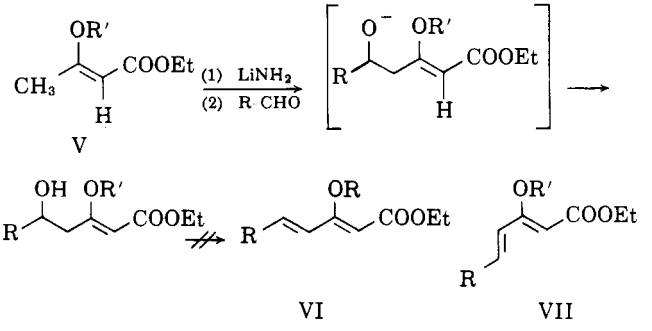


II

As a model reaction, a sample of ethyl β-methoxy-*cis*-crotonate (which was impure as is shown by the n.m.r. spectrum described above) was allowed to react with 2 equiv. of lithium amide in liquid ammonia followed by 1 equiv. of benzaldehyde. The excess lithium amide was employed, as previously discussed, to prevent self-condensation of the ester. Upon acidification and work up, a considerable amount of crystalline material was obtained. This material gave a negative ferric chloride test, but was soluble in dilute sodium carbonate. Infrared spectroscopy together with qualitative tests indicated that the crystalline material was the unsaturated acid, IVa, rather than the desired dihydropyrone, Ia.

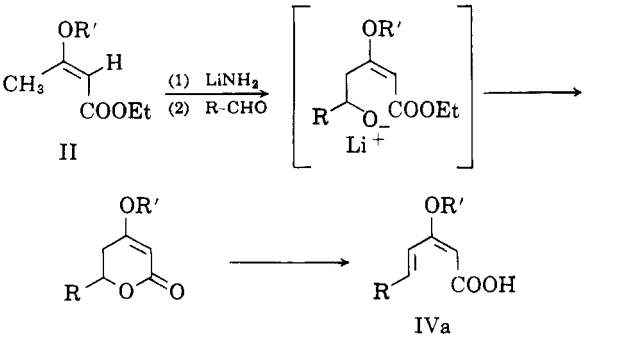
The use of other aldehydes or of ethyl β-ethoxy-*cis*-crotonate (III) gave unsaturated acids whose physical and chemical properties could be correlated with reported acids, shown in Table II. Further support of the configuration of these acids was obtained by comparing n.m.r. spectra, shown in Fig. 3 and 4. There is substantial literature on the n.m.r. characteristics of *cis–trans* isomers of the types represented by II, III, IV, VI, and VII.[9] The assignments given herein are in agreement with those reported by Wiley and coworkers. The low-field doublets (487–471 c.p.s. in the spectrum of 3-methoxy-5-phenyl-*cis*-2-*trans*-4-pentadienoic acid and 488–472 c.p.s. in 3-ethoxy-5-phenyl-*cis*-2-*trans*-4-pentadienaoic acid) with $J = 16$ is consistent only with the 2-*cis*-4-*trans* configuration as shown by Wiley[9d] in 3-methyl-5-aryl-2,4-pentadienoic acids.

It is possible but unlikely that the *trans* crotonate, V (methyl and carboxyl groups *trans*), would yield a *cis–trans* unsaturated acid, IVa, as it would necessitate a configurational change around the 2,3 double bond. The fact that no esters (VI or VII) were isolated also suggests that the alkoxy crotonates do not possess the



V VI VII

trans configuration. However, the *cis* isomer, II, is capable of condensing with an aldehyde followed by lactonization owing to the juxtaposition of the ester function.



II IVa

It is evident, therefore, that intrinsically the dihydropyrones had been produced, but, owing to the basic reaction conditions, the lactone ring was opened yielding the *cis–trans* unsaturated acids. In order to determine the base responsible for this ring opening, kawain

(9) (a) R. H. Wiley, P. F. G. Nau, and T. H. Crawford, *J. Org. Chem.*, **26**, 4285 (1961); (b) R. H. Wiley, T. H. Crawford, and C. E. Staples, *ibid.*, **27**, 1535 (1962); (c) R. H. Wiley, P. F. G. Nau, H. C. van Der Plas, and T. H. Crawford, *ibid.*, **27**, 1962; (d) R. H. Wiley, H. C. van Der Plas, and N. F. Bray, *ibid.*, **27**, 1989 (1962); (e) R. H. Wiley and C. E. Staples, *ibid.*, **28**, 3408 (1963); (f) *ibid.*, **28**, 3413 (1963).

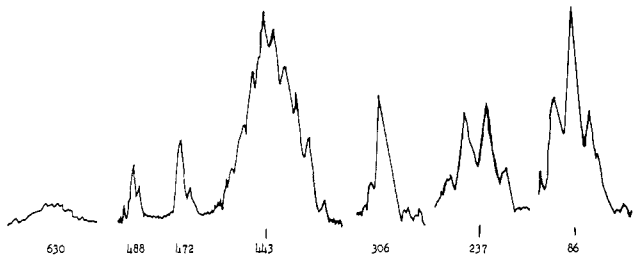


Fig. 3.—N.m.r. spectrum of 3-ethoxy-5-phenyl-*cis*-2-*trans*-4-pentadienoic acid determined in deuteriochloroform (c.p.s.).

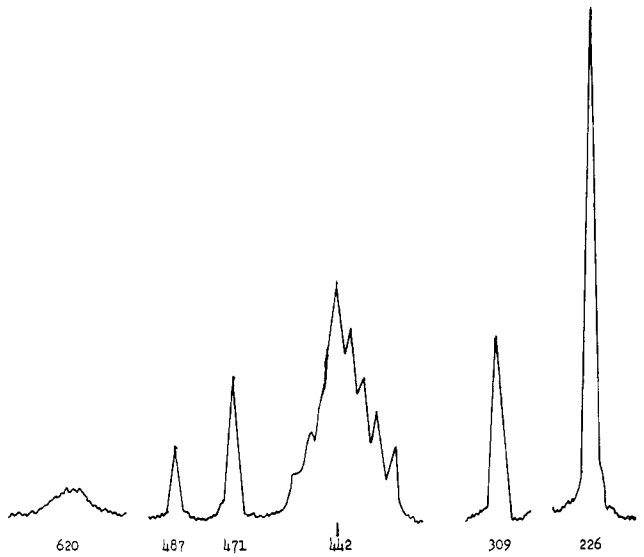
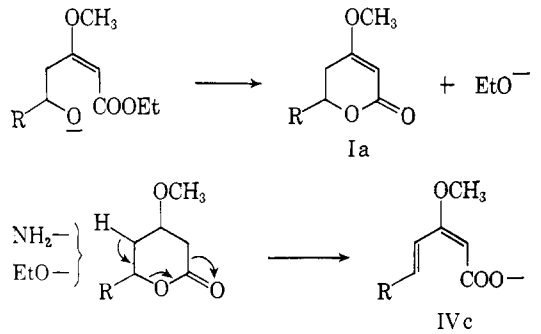


Fig. 4.—N.m.r. spectrum of 3-methoxy-5-phenyl-*cis*-2-*trans*-4-pentadienoic acid determined in deuteriochloroform (c.p.s.).

(Ia) was suspended in liquid ammonia for 2 hr. Evaporation of the ammonia yielded unchanged kawain. Thus the liquid ammonia was not responsible for the facile ring opening, and either the amide ion or the generated alkoxide ion, or both, must be the base or bases responsible. This was proven by allowing kawain (Ia) to react with 2 equiv. of lithium amide in liquid ammonia for 1 hr. After work-up kawaic acid (IVa) was obtained in essentially quantitative yield.



Attempts to prevent the ring opening by using equivalent quantities of lithium amide and crotonate or a very short reaction time afforded no lactone and served only to decrease the yield of unsaturated acid.

Experimental[10]

Ethyl β-Ethoxy-*cis*-crotonate (III).—This material was prepared by the procedure of Blaise and Marie.[8] In a 50-ml., pear-shaped flask was placed 13.0 g. (0.1 mole) of ethyl acetoacetate and 15.1 g. (0.102 mole) of triethyl orthoformate. Concentrated sulfuric acid (3 drops) was added and the mixture was allowed to stand at room temperature for 24 hr. A slight excess of quinoline (*ca.* 6 drops) was added to neutralize the sulfuric acid. Distillation of the dark mixture under reduced pressure afforded 14 g. (89%) of ethyl β-ethoxy-*cis*-crotonate (III), b.p. 90–92° (15 mm.) [lit.[8] b.p. 195–200° (760 mm.)].

This liquid crystallized at room temperature and gave a negative ferric chloride (enol) test. The infrared spectrum (chloroform) showed strong absorption at 5.9 (conjugated ester) and 6.2 μ (C=C). The n.m.r. spectrum of this material is shown in Fig. 1 and discussed in the text.

Ethyl β-Methoxy-*cis*-crotonate (II).—The procedure for the preparation of ethyl β-ethoxy-*cis*-crotonate (III) was followed using 52.0 g. (0.4 mole) of ethyl acetoacetate, 43.0 g. (0.405 mole) of trimethyl orthoformate, 5 drops of concentrated sulfuric acid, and 10 drops of quinoline. Distillation afforded 54.6 g. (95%) of ethyl β-methoxy-*cis*-crotonate (II), b.p. 70–72° (13 mm.) [lit.[2] b.p. 188–193° (760 mm.)]. This liquid gave a negative ferric chloride (enol) test and showed strong absorption in the infrared (chloroform) at 5.8 (ester) and 6.15 μ (C=C). The n.m.r spectrum (Fig. 2) of this liquid suggested that it was not homogeneous, as discussed in the text. After several distillations at atmospheric pressure a small amount of the pure crotonate II was obtained.

Anal. Calcd. for $C_7H_{12}O_3$: C, 58.31; H, 8.39; CH_3O, 21.53. Found: C, 58.52; H, 8.24; CH_3O, 28.00.

3-Ethoxy-5-phenyl-*cis*-2-*trans*-4-pentadienoic Acid (IVb).—The suspension of 0.2 mole of lithium amide in 300 ml. of anhydrous liquid ammonia was prepared as in previous reactions. To this suspension was added a solution of 15.8 g. (0.1 mole) of ethyl β-ethoxy-*cis*-crotonate (III) in 20 ml. of dry ether and stirring was continued for 10 min. A solution of 10.6 g. (0.1 mole) of freshly distilled benzaldehyde in 20 ml. of dry ether was added, stirring was continued for 1 hr., and the ammonia was expelled by means of a hot-water bath as an equal volume of ether was added. The ether was allowed to reflux for 5 min., 200 ml. of ice–water was added, and the mixture was transferred to a separatory funnel. The aqueous solution was extracted three times with 50-ml. portions of ether and the ether solutions were discarded. After cooling to 5° in an ice bath, the aqueous solution was made acidic (pH 6) with 5% hydrochloric acid and the white precipitate was filtered. Two recrystallizations from alcohol–water yielded 16 g. (74%) of 3-ethoxy-5-phenyl-*cis*-2-trans-4-pentadienoic acid (IVb), m.p. 151–152° dec. (lit.[11] m.p. 153–154° dec.). The ultraviolet absorption is described in Table II and the n.m.r. spectrum is shown in Fig. 3. These long white crystals were soluble in dilute sodium carbonate solution, gave a negative ferric chloride (enol) test, and showed medium infrared absorption (Nujol mull) at 6.0 (conjugated acid) and 14.35 μ (monosubstituted benzene).

Anal. Calcd. for $C_{13}H_{14}O_3$: C, 71.58; H, 6.46. Found: C, 71.57; H, 6.34.

To a solution of 60 mg. of 2,4-dinitrophenylhydrazine dissolved in 1.0 ml. of methanol and 10.0 ml. of 1 *N* hydrochloric acid was added 50 mg. of the dienoic acid, IVb. The mixture was heated to boiling for 2 min. and the resulting flocculent precipitate was collected on a Büchner funnel. Recrystallization from alcohol–water afforded a bright red hydrazone, m.p. 221–222° (lit.[11] m.p. 221–222° for the 2,4-DNP of benzalacetone).

3-Methoxy-5-phenyl-*cis*-2-*trans*-4-pentadienoic Acid (IVa).—The procedure for the preparation of 3-ethoxy-5-phenyl-*cis*-2-*trans*-4-pentadienoic acid (IVb) was followed using 0.2 mole of lithium amide in 300 ml. of anhydrous liquid ammonia, 14.4 g. (0.1 mole) of crude ethyl β-methoxy-*cis*-crotonate (II), and 10.6 g. (0.1 mole) of freshly distilled benzaldehyde. After two recrystallizations from alcohol–water, 15 g. (74%) of the dienoic acid (IVa) was obtained, m.p. 157.5–158° dec., m.p. 171–172° dec. (hot stage) [lit.[12] m.p. 173° dec. (hot stage)]. This crystalline material was soluble in dilute sodium carbonate solution and gave a negative ferric chloride (enol) test. The acid exhibited infrared absorption (Nujol mull) at 5.95 (conjugated acid) and 14.43 μ (monosubstituted benzene). The ultraviolet absorption is

(10) Melting points were obtained on a calibrated Thomas–Hoover Unimelt and are corrected. Infrared data were recorded on Beckman IR5 and IR8 spectrophotometers. Nuclear magnetic resonance data were recorded on a Varian Associates Model A-60 spectrophotometer using tetramethylsilane as the internal standard. Ultraviolet data were recorded on a Bausch and Lomb 505 spectrophotometer. Microanalyses were conducted by Dr. G. Weiler and Dr. F. B. Strauss, Oxford, England.

(11) See Table II, footnote *b*.

(12) See Table II, footnote *a*.

described in Table II. The n.m.r. spectrum is shown in Fig. 4. The 2,4-DNP derivative was prepared as described previously, m.p. 221–222° (lit.[11] m.p. 221–222° for the 2,4-DNP of benzalacetone).

Anal. Calcd. for $C_{12}H_{12}O_3$: C, 70.58; H, 5.92; CH_3O, 15.20. Found: C, 70.20; H, 5.70; CH_3O, 14.93.

In an attempt to prevent ring opening, 14.4 g. (0.1 mole) of crude ethyl β-methoxy-*cis*-crotonate was added to a suspension of 0.12 mole of lithium amide in 300 ml. of anhydrous liquid ammonia. The mixture was stirred for 0.5 min., followed by the addition of 10.6 g. (0.1 mole) of freshly distilled benzaldehyde. Stirring was continued for 5 min., 6.5 g. (0.12 mole) of solid ammonium chloride was added, and the work-up was the same as for the preparation of (IVb). After one recrystallization from alcohol water, 6 g. (30%) of the dienoic acid (IVa) was obtained, m.p. 157.5–158° dec. This crystalline material gave an infrared spectrum identical with that of the dienoic acid (IVa).

3-Methoxy-7-phenyl-*cis*-2-*trans*-4,6-heptatrienoic Acid (IVc, Kavaic Acid).—The procedure for the preparation of 3-ethoxy-5-phenyl-*cis*-2-*trans*-4-pentadienoic acid (IVb) was followed using 0.2 mole of lithium amide in 300 ml. of anhydrous ammonia, 14.4 g. (0.1 mole) of crude ethyl β-methoxy-*cis*-crotonate, and 13.2 g. (0.1 mole) of freshly distilled *trans*-cinnamaldehyde. After two recrystallization from 95% alcohol, 12 g. (52%) of kavaic acid (IVc) was obtained, m.p. 178–178.5° dec. (lit.[13] m.p. 184° dec.).

The yellow crystalline material was soluble in dilute sodium carbonate solution and gave a negative ferric chloride (enol) test. The 2,4-DNP derivative was prepared as described previously, m.p. 217–217.5 (lit.[14] m.p. 218–220°, cinnamal-acetone). The infrared spectrum (Nujol mull) exhibited absorption at 5.95 (conjugated acid) and 14.6 μ (monosubstituted benzene). The ultraviolet absorption is described in Table II.

Anal. Calcd. for $C_{14}H_{14}O_3$: C, 73.02; H, 6.13; CH_3O, 13.48. Found: C, 72.84; H, 5.91; CH_3O, 14.52.

An authentic sample of kavaic acid was prepared by adding 0.23 g. (0.001 mole) of kavain[15] to a suspension of 0.002 mole of lithium amide in 50 ml. of anhydrous liquid ammonia. The kavaic acid was isolated as described above and recrystallized twice from absolute methanol, m.p. 184° dec. (lit.[13] m.p. 184° dec.). The admixture melting point of authentic kavaic acid 184° dec.) and kavaic acid (IVc, m.p. 178–178.5° dec.) was 179° dec. This authentic sample of kavaic acid exhibited absorption in the ultraviolet at the following wave lengths: λ_{max}^{EtOH} 244 (ε 8320), 251 (9570), and 332 mμ (41,900) [lit.[13] λ_{max}^{EtOH} 251 (ε 9500) and 332 mμ (40,000)].

5,5-Diphenyl-3-ethoxy-4-*cis*-2-pentadienoic Acid (IVd).—The procedure for the preparation of 3-ethoxy-5-phenyl-*cis*-2-*trans*-4-pentadienoic acid (IVb) was followed using 0.2 mole of lithium amide in 300 ml. of anhydrous liquid ammonia, 15.8 g. (0.1 mole) of ethyl β-ethoxy-*cis*-crotonate, and 18.2 g. (0.1 mole) of benzophenone. After two recrystallizations from alcohol–water, 12 g. (41%) of the dienoic acid IVd was obtained, m.p. 149.5° dec. The long, white crystalline rods were soluble in dilute sodium carbonate solution and gave a negative ferric chloride (enol) test.

Anal. Calcd. for $C_{19}H_{18}O_3$: C, 77.53; H, 6.16. Found: C, 77.27; H, 6.17.

3-Methoxy-7-*cis*-2-*trans*-4-heptadienoic Acid (IVe, Dihydrokavaic Acid).—The procedure for the preparation of 3-ethoxy-5-phenyl-*cis*-2-*trans*-4-pentadienoic acid (IVb) was followed using 0.2 mole of lithium amide in 300 ml. of anhydrous liquid ammonia, 14.4 g. (0.1 mole) of crude ethyl β-methoxy-*cis*-crotonate, and 13.4 g. (0.1 mole) of hydrocinnamaldehyde. After two recrystallizations from alcohol–water, 1.4 g. (6%) of the trienoic acid IVe was obtained, m.p. 137.5–138° dec. (lit.[14] m.p. 139–140° dec.). This crystalline material was soluble in dilute sodium carbonate solution and gave a negative ferric chloride (enol) test. The infrared spectrum (chloroform) exhibited absorption at 5.98 (C=O) and 6.1 μ (C=C).

Anal. Calcd. for $C_{14}H_{16}O_3$: C, 72.40; H, 6.94. Found: C, 72.46; H, 7.09.

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(13) See Table II, footnote *c*.

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(15) The authors are grateful to Smith, Kline and French Laboratories for generously providing a sample of kavain.

Synthesis of a Homolog of Aspergillic Acid

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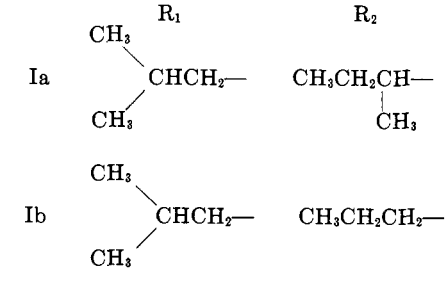
The 6-propyl homolog of aspergillic acid was synthesized. N-Leucyl-O-benzylhydroxylamine, prepared by reaction of phthalylleucyl chloride with O-benzylhydroxylamine, followed by treatment with hydrazine hydrate, was treated with 1-chloro-2-pentanone oxime; the product was hydrolyzed to give N-[4-methyl-2-(2-oxopentylamino)valeryl]-O-benzylhydroxylamine, which was catalytically hydrogenated to give the corresponding hydroxamic acid. The open-chain hydroxamic acid was cyclized by means of treatment with ammonia to yield 1-hydroxy-3-isobutyl-6-propyl-2-pyrazinone.

Aspergillic acid, an antibiotic isolated by White and Hill[1] from the culture filtrates of *Aspergillus flavus*, has been concluded by Dutcher[2] and Newbold, *et al.*,[3] to be 1-hydroxy-3-isobutyl-6-*sec*-butyl-2-pyrazinone or its tautomeric 1-oxide of the 2-hydroxypyrazine (Ia). Hydroxyaspergillic acid isolated by Menzel[4] and mutaaspergillic acid isolated recently by Nakamura[5] have



been shown to be also 3,6-disubstituted 1-hydroxy-2-pyrazinones.

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Results and Discussion

Two syntheses of 3,6-disubstituted cyclic pyrazine-hydroxamic acids have been described. Reaction of aminoacetone with the bisulphite derivative of pyruvohydroxamic acid gave 1-hydroxy-3,6-dimethyl-2-pyr-